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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,622	06/27/2005	Giulio Alessandri	47706	2850

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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,622	ALESSANDRI ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 6/26/08 to claims 1, 2, and 8 have been entered. No claims have been cancelled or added. Claims 1-14 remain pending in the current application, of which claims 1, 2, and 7-9 are being considered on their merits. Claims 3-6 and 10-14 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 7-9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in

the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are drawn to a method of making stem cells by preparing a suspension of cells from human adipose tissue and culturing the cells in a medium comprising bovine serum albumin (BSA), four growth factors (bFGF, EGF, VEGF, and LIF), heparin, and other components. In some dependent claims, the amounts of components added to the media are particularly pointed out. In some dependent claims, the cells are incubated on a collagen-coated culture dish and then on a non-coated dish.

Adipose stromal cells were known at the time of the invention to be a source of stem cells. Zuk et al. (2002, *Molecular Biology of the Cell* 13: 4279-4295; IDS) teach washing lipoaspirate with PBS, treating said lipoaspirate with collagenase, and culturing the cells freed by the collagenase action in DMEM supplemented with FBS (page 4280 and Table 1).

Adding growth factors and other active agents to cultures of primary cells isolated from adipose is known to alter the differentiation state of the cells. Hauner et al. (2001, *Methods in Molecular Biology* 155: 239-247; IDS) teach that culturing cells dissociated from adipose tissue in medium comprising insulin promotes differentiation of the cells to adipocytes (page 243, section 3.6, item 2). Hauner (2001) further teaches that incubating adipose stromal cells with FGF promotes adipocyte differentiation (page 243,

section 3.5). Hauner et al. (1995, *European Journal of Clinical Investigation* 25: 90-96; IDS) teaches that EGF modulates the differentiation state of primary adipocyte precursor cells (page 90, column 2). Zhao et al. (1997, *Journal of Steroid Biochemistry and Molecular Biology* 61: 203-210; reference U) teach that LIF induces adipose stromal cells to begin synthesizing estrogen *in vitro* (Abstract and page 204, column 2). Amri et al. (1986, *Biochemical Journal* 238: 115-122; reference V) teach that putrescine promotes differentiation of adipose stromal cells to mature adipocytes (Abstract and Figure 1, e.g.). Investigations published after the instant filing indicate that the skilled artisan would not have had a reasonable expectation of using the instantly recited method to yield stem cells from adipose. Song et al. (2007, *Biochemical and Biophysical Research Communications* 354: 999-1003; reference W) teach that adipose stromal cells cultured in VEGF spontaneously differentiate into cardiomyocytes (Abstract and page 1003, column 1).

At the time of the invention, skilled artisans recognized that the particular composition of the medium in which adipose stromal cells are cultured affects the differentiation state of the cells. However, the effect of a particular active agent added to the medium in which stromal cells are cultured on the differentiation state of the cells was not predictable at the time of the invention. The guidance in the specification provides insufficient evidence that the skilled artisan would have reasonably expected to obtain undifferentiated stem cells that retain the ability to differentiate into nerve cells, vascular cells, and bone cells from adipose tissue. The specification describes the

properties of cells obtained using the instantly claimed steps on muscle tissue, but the working examples include no characterization of cells obtained from adipose tissue.

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)...In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." As the above discussion illustrates, the effects of at least a few active agents on adipose stromal cells were unpredictable at the time of the invention, so addition of any given active agent or combination thereof to adipose stromal cells must be considered "nascent," and the amount of guidance required is relatively high.

The specification reads, "Because the [human fat stem cells] of the present invention are of the same mesenchymal origin as the [human muscle stem cells], this also suggests that the same differentiating abilities described above contained in the hMSC are also present in the hFSC" (page 11, paragraph 5). However, this statement is not supported by evidence. Numerous diverse tissues including connective tissue, bone, cartilage, and blood, as well as the tissues that make up the circulatory and lymphatic systems, arise from mesenchyme. These tissues do not share functions with each other or with adipose and/or skeletal muscle, and they do not contain the same kinds of cells. The specification provides no evidence that all tissues of mesenchymal origin may be cultured in the instantly claimed culture medium to yield undifferentiated stem cells.

While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Applicant supplies two prior art references that allegedly support their argument that the instantly claimed method is enabled (Remarks, first page, second paragraph). These arguments have been fully considered, but they are not persuasive.

As discussed above, the effects of particular growth factors on cells in the stem cell production art are unpredictable. This rejection does not seek to establish that at the time of filing, obtaining stem cells from adipose tissue would have required undue

experimentation; indeed, at page 3, paragraph 3, of the 3/14/08 Office action, the examiner indicated that such methods are known. What is at issue in this rejection is whether cells made by the instantly claimed method, which requires incubating tissue with numerous growth factors, are truly stem cells. As reviewed within the rejection, the components necessarily required in the medium used for applicant's method were known at the time of the invention to have effects on the differentiation state of cells obtained from adipose tissue. There is no evidence or persuasive argument on the record in this case that the particular growth factor combination required for the method of claim 1 would yield stem cells. The basis of this rejection is that given the fact that growth factors were known at the time to promote differentiation of cells isolated from adipose tissue, the skilled artisan would not necessarily have concluded that cells made by applicant's method are truly stem cells. The examiner emphasizes again for the record that the specification includes no data regarding the differentiation state of cells made by the instant method, but rather only speculates that since muscle and adipose come from the same germ layer, cells isolated from one would behave similarly to cells isolated from the other. There is no evidence on the record that this is the case.

The Mizuno reference has been carefully considered, but it does not appear to teach the same steps as those instantly claimed. Mizuno teaches culturing processed lipoaspirate in DMEM supplemented with serum (page 200, column 2). It is not clear how the Mizuno reference relates to the instantly recited steps. Similarly, Asakura does not employ adipose tissue at all; this reference does not appear to be pertinent to the elected species, i.e. a method for making stem cells from adipose tissue.

It is noted that applicants allegedly possess data in support of patentability (Remarks, first page, last paragraph). It is not clear, however, why this data was not presented with the instant reply. Evidence can and should be submitted to overcome enablement rejections, not only to overcome utility rejections. If applicants possess evidence that cells made by the instantly claimed method are truly stem cells, that evidence could be persuasive to overcome this rejection.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. **A copy of such copending claims is requested in response to this Office action.**

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651